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Analgesic, Anti-tumor, Antiarrhythmic, Anti-inflammatory, and CNS Inhibitory Activities of Oxysophoridine

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Abstract This paper review summarizes the analgesic, anti-tumor, antiarrhythmic, anti-inflammatory, and CNS inhibitory activities of oxysophoridine, along with their underlying molecular mechanisms. In terms of analgesic activity, oxysophoridine exerts pain relieving effects by enhancing GABAergic inhibitory function. Regarding anti-tumor activity, its combination with salvianolic acid A can synergistically block the cell cycle, induce apoptosis, and inhibit the proliferation of cervical precancerous cells. With respect to antiarrhythmic activity, it acts through non specific antagonism of the adrenergic system and blockade of sodium ion influx. As for anti-inflammatory activity, it downregulates CD14/TLR4 expression, inhibits pathways such as NF-κB, and reduces the release of inflammatory cytokines. Furthermore, in its CNS inhibitory activity, it dose-dependently suppresses spontaneous locomotor activity in mice and synergistically enhances hypnotic effects. This review provides a theoretical basis for the further development and clinical application of oxysophoridine.

Key words Oxysophoridine, Analgesic activity, Anti-tumor activity, Antiarrhythmic activity, Anti-inflammatory activity, CNS inhibitory activity

1 Introduction

Sophora alopecuroides L., a plant of the genus *Sophora* in the family Fabaceae[1], is distributed across multiple provinces in China and possesses effects of clearing heat, removing toxicity, drying dampness, and relieving pain[2]. *Sophora* species are an important component of medicinal plant resources and are frequently used in the treatment of a variety of diseases. Oxysophoridine (OSR) is a quinolizidine alkaloid extracted from *S. alopecuroides* L. Its molecular formula is $C_{15}H_{24}N_2O_2$, and it is soluble in organic solvents such as methanol, ethanol, and DMSO. Oxysophoridine exhibits a range of pharmacological activities, including analgesic, antitumor, antiarrhythmic, anti-inflammatory, and CNS inhibitory activities. This article reviews the pharmacological activities of oxysophoridine and their underlying molecular mechanisms reported in recent years, with the aim of providing a theoretical basis for further research and clinical application of OSR.

2 Analgesic effects

Analgesia is the core intervention for pain relief and alleviation in medicine, pharmacy and nursing. If long-term analgesia is not handled properly, it will not only aggravate kidney damage, increase cardiovascular risk, but also lead to drug dependence. Therefore, it is of great clinical significance to develop safe and potent new analgesic drugs. It has been found that OSR has a good analgesic effect.

Cheng Fan *et al.*[3] examined changes in the mechanical pain threshold in mice following administration of different doses of OSR using behavioral pharmacology assays. The results showed that medium and high doses of OSR significantly and dose-dependently elevated the pain threshold, with the peak analgesic effect observed at 120 min, whereas the low dose was ineffective. These findings indicate that OSR possesses a clear and potent analgesic activity in a dose-dependent manner. Further co-administration experiments with GABAergic system tool drugs were conducted to assess the analgesic effect of OSR in combination with GABA, GABA reuptake inhibitors, and GABA receptor agonists/antagonists. The results revealed that the analgesic activity of OSR relied entirely on intact GABAergic neural function, indicating that the GABAergic system is an indispensable core downstream pathway for its analgesic activity. Subsequently, double immunofluorescence staining for c-Fos/GAD67 and c-Fos/GAT-1 was used to examine the co-expression of GABA-synthesizing enzyme and transporter in pain-activated neurons. The results demonstrated that OSR upregulated the expression of the GABA-synthesizing enzyme GAD67 while downregulating the expression of the GABA transporter GAT-1 in activated neurons, indicating that OSR bidirectionally regulates GABAergic neuronal function at the cellular and molecular level. This suggests that OSR enhances GABA biosynthesis and inhibits its reuptake, thereby specifically augmenting GABAergic inhibitory tone in pain-related brain regions. In summary, OSR enhances central GABAergic inhibitory function and significantly elevates the pain threshold over time, thereby producing analgesic effects in mouse models of neuropathic pain. These findings demonstrate that OSR possesses potent analgesic activity and holds promise for development as a novel analgesic drug.

3 Anti-tumor effects

Cancer refers to the characteristics of gene mutation, loss of normal regulation, invasion and destruction of surrounding tissues and distant metastasis of cells in vivo. Cancer cells can overcome the

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adhesion between cells, further migrate, invade, and eventually metastasize to other sites, so clinical treatment is relatively difficult. Studies have found that OSR has a good inhibitory effect on rectal cancer.

Leng Xuejiao *et al.* [4] examined the synergistic mechanism of salvianolic acid A (SAA) combined with oxysophoridine (OSR) against cervical precancerous lesions using morphological observation and Hoechst 33342 staining. The combination group showed that H8 cervical epithelial immortalized cells became smaller, rounder, and largely detached, with markedly poor adhesion, indicating a synergistic disruption of cell architecture by SAA and OSR. Cell cycle distribution analysis by flow cytometry revealed that OSR alone and the combination group both arrested H8 cells in the G_2/M phase; notably, the combination exerted a significantly stronger arrest than either single agent, implying that the two drugs synergistically block cell cycle progression into mitosis and thereby inhibit proliferation. Western blotting was further employed to measure the expression of apoptosis- and cell cycle-related key proteins. Both agents alone downregulated the anti-apoptotic protein Bcl-2 and upregulated the pro-apoptotic Bax and cleaved Caspase-3. The combination further enhanced the downregulation of Bcl-2 and the upregulation of Bax/cleaved Caspase-3, demonstrating a dual synergistic effect at the molecular level, promoting apoptosis while simultaneously suppressing cell cycle engine proteins. In conclusion, SAA and OSR powerfully inhibit cervical precancerous cells through synergistic cell cycle arrest and synergistic induction of apoptosis, indicating that SAA and OSR can suppress the proliferation of cervical precancerous/cancer cells and effectively delay the progression of cervical cancer, thereby holding promise for development as novel drugs for cervical cancer.

4 Antiarrhythmic effects

Arrhythmia refers to the pathological phenomenon that the frequency and rhythm of heart activity are disturbed[5]. A type of heart disease in which the origin, frequency, rhythm, or conduction pathway of the heart is disturbed, resulting in a fast, slow, irregular, or premature heartbeat. Studies have shown that OSR has a good inhibitory effect on arrhythmia.

Zhang Mingfa *et al.* [6] used electrophysiological recordings from mouse isolated atria and papillary muscles to evaluate the effects of OSR on spontaneous rate, automaticity, excitability, refractory period, and action potential configuration. The results revealed that OSR decreased heart rate, suppressed abnormal automatic rhythms, and prolonged the effective refractory period. These findings indicate that OSR blocks sodium ion entry into cardiomyocytes and thereby exerts antiarrhythmic activity. Further experiments explored the drug's influence on the adrenergic system. OSR antagonized the positive chronotropic effect of the β-receptor agonist isoproterenol, producing a rightward shift of the dose-response curve; however, it did not competitively inhibit β-receptors, indicating that OSR acts through non-specific antagonism of adrenergic excitation. In addition, OSR produced a dose-dependent positive inotropic effect on papillary muscle contractility, showing that it possesses both cardiotonic and antiarrhythmic properties. Taken together, OSR represents a natural antiarrhythmic agent with a distinctive multi-target profile, fundamentally different from most established antiarrhythmic drugs. Through non-specific antagonism of adrenergic system excitation, OSR indirectly shields the heart from arrhythmias induced by excessive sympathetic drive. Its combined effects on contractility and rhythm suggest that it may be particularly advantageous for arrhythmia patients with concurrent heart failure, holding considerable promise as a novel therapeutic for arrhythmias.

5 Anti-inflammatory effects

Inflammation is the defense reaction of vascular system and living tissue to injury factors, which is a very common and important basic pathological process. Prolonged infection and inflammation can lead to immune disorders, organ damage and even premature aging. Studies have shown that OSR has good anti-inflammatory effect.

Zhang Mingfa *et al.* [6] evaluated the anti-inflammatory effects of OSR in several acute and chronic inflammation animal models following intraperitoneal administration, with a focus on the lipopolysaccharide (LPS)-induced lung injury model in mice. The results showed that OSR dose-dependently suppressed these inflammatory responses, attenuating tissue edema, inflammatory cell infiltration, and pathological damage, demonstrating broad-spectrum anti-inflammatory activity against both endotoxic and chemical inflammation. *In vitro*, OSR significantly inhibited the release of key inflammatory mediators (TNF-α, IL-1β, and NO) from LPS-stimulated macrophages. Mechanistically, it downregulated the expression of the pattern recognition receptors CD14 and TLR4, thereby inhibiting two core inflammatory signaling pathways. These findings indicate that OSR exerts its anti-inflammatory effects through multi-target modulation of the inflammatory signaling network, regulating events from receptors and pathways to terminal effector molecules. Additional immune functional assays revealed that in immunosuppressed animals, OSR enhanced macrophage phagocytosis and antibody production, while in the context of excessive immune activation it displayed inhibitory effects. This bidirectional profile suggests that OSR acts as an immunomodulator, restoring immune balance rather than simply suppressing immune responses. Taken together, OSR represents a natural anti-inflammatory and immunomodulatory agent with a unique multi-target mechanism. It exerts potent inflammation-relieving effects and shows promise for development as a novel anti-inflammatory drug.

6 Central nervous system inhibitory effect

The central nervous system is the advanced center of the body's nerve integration and regulation, which is composed of the brain and spinal cord, located in the cranial cavity and spinal canal, responsible for perception, integration, motor instructions and the implementation of advanced nerve functions. It has been found

that OSR has inhibitory effect on the central nervous system.

Yu Jianqiang *et al.* [7] administered different doses of OSR to mice, observed their appearance and behavioral manifestations, and recorded the number of spontaneous locomotor activities within 10 min. The results showed that the drugtreated mice exhibited reduced activity, lying still with eyes closed, and sluggish responses. Photoelectric counting revealed that the number of spontaneous locomotor activities decreased significantly in a dosedependent manner (250, 500, and 1 000 mg/kg), indicating that OSR markedly suppressed spontaneous exploratory behavior and exerted central inhibitory and sedative effects. In addition, a synergistic hypnotic experiment with pentobarbital sodium was conducted in mice to observe the influence on the hypnotic effect of pentobarbital sodium and the synergistic effect at a subthreshold hypnotic dose, and to record sleep latency, sleep duration, and the rate of induced sleep. The results showed that OSR significantly shortened sleep latency, significantly prolonged sleep duration, and, when combined with a certain dose (40 mg/kg) of pentobarbital sodium, induced sleep in more than half of the animals, indicating that OSR itself possesses hypnotic potential and can enhance the hypnotic effect of central depressants. Its sedativehypnotic effect is related to the activation or enhancement of endogenous sleep/inhibitory neural pathways, and a significant synergistic effect exists. Further, a pentylenetetrazol (PTZ) induced convulsion antagonism experiment was performed to observe the protective effect of the drug against clonic convulsions induced by the chemical convulsant PTZ. The results revealed that OSR did not significantly reduce the number of animals developing PTZ induced convulsions, indicating that its central inhibitory action is pathwayselective, primarily affecting mechanisms related to sedation and hypnosis, while exhibiting no significant effect on convulsive pathways associated with the targets of PTZ. In summary, OSR is a natural compound with clear central inhibitory activity, demonstrating that OSR exerts inhibitory effects on the central nervous system and holds promise for development as a novel hypnotic drug.

7 Conclusions and prospects

OSR exhibits significant multiple pharmacological activities, including analgesic, antitumor, antiarrhythmic, anti-inflammatory, and CNS inhibitory activities. In particular, it exerts favorable inhibitory effects on tumor cell proliferation, migration, and invasion, holding broad prospects for drug development and clinical application. However, as a natural compound derived from traditional Chinese medicine, research on its pharmacological mechanisms and clinical application remains at a preliminary stage. It is therefore necessary to continually integrate knowledge, theories, and experimental techniques from disciplines such as molecular biology, cell biology, laboratory animal science, pharmacology, and basic medicine, and to conduct more comprehensive and in-depth investigations of OSR at the molecular, cellular, and animal levels, so as to elucidate its precise molecular targets and regulatory signaling networks. These efforts will provide a theoretical basis and data support for the future development of OSR-based herbal preparations, clinical translation, and the design of rational combination drug regimens.

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